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(54) Title: CHOLINESTERASE INHIBITORS TO PREVENT INJURIES CAUSED BY CHEMICALS

(57) Abstract: The invention provides methods for treating and preventing injuries caused by chemicals by administering to a patient a therapeutically effective amount of at least one cholinesterase inhibitor. The chemicals can be, for example, agricultural compounds or chemical weapons. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

WO 03/092606 A2

Cholinesterase Inhibitors to Prevent Injuries Caused By Chemicals

Related Application

This application claims priority to US Provisional Application No. 60/376,560 filed May 1, 2002, which is incorporated herein by reference.

Field of the Invention

The invention provides methods for treating and preventing injuries caused by chemicals by administering to a patient a therapeutically effective amount of at least one cholinesterase inhibitor. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

Background of the Invention

Often referred to as the "poor man's nuclear weapon," chemical and biological weapons of war are so named because they cost much less than real nuclear weapons to develop, do not require a high level of technology to produce, and can potentially kill enormous numbers of people. Indeed, unlike nuclear weapons, which require a large, specialized, and costly scientific-industrial base, chemical and biological agents can be made with commercial equipment generally available to any country. Weapons of this sort are especially attractive for use by developing countries against super powers, as they tend to level the playing field in struggles against these better armed and trained opponents. The use of biological and chemical weapons of mass destruction is banned by international treaty, but reports of suspected and confirmed use continue. The threat and fear of the possible use of biological and chemical weapons against United States citizens and the United States Armed Forces has been particularly high since the attacks on the United States on September 11, 2001.

Among lethal chemical warfare agents, nerve gases have played a dominant role since the Second World War. Nerve gases are so-called because they affect the transmission of nerve impulses within the nervous system. Nerve gases belong chemically to the group of organophosphorus compounds. Organophosphorus compounds are stable, easily dispersed, highly toxic, and take effect rapidly both when absorbed through the skin and via respiration. They can be manufactured by means of fairly simple chemical techniques and the raw materials to manufacture them are inexpensive and generally readily available. Sarin, one of the more familiar nerve gases, dates from the Second World War. In the mid-1950's, a group of more stable nerve gases known as V-agents were developed, with VX being one of the more successful variants. These later-day chemical weapons are approximately ten-fold more poisonous than sarin and are thus among the most toxic substances ever synthesized.

Nerve gases in the pure state are colorless liquids with volatiles that vary depending on the particular compound. The consistency of VX may be likened to a non-volatile oil and is classified as belonging to a group of persistent chemical warfare agents. It enters the body mainly through direct

contact with the skin. Sarin is at the opposite extreme, being a relatively volatile liquid, and is mainly taken up through the respiratory organs.

Nerve gases, either as a gas, aerosol or liquid, enter the body through inhalation or through the skin. Poisoning may also occur through consumption of liquids or foods contaminated with nerve gases. The route through which the poison enters the body largely determines the time required for the nerve gases to begin having an effect. It also influences the symptoms developed and, to some extent, the sequence of the different symptoms. Generally, poisoning takes place more rapidly when the nerve gas is absorbed through the respiratory system than when it enters via other routes such as the skin. This is because the lungs contain numerous blood vessels which provide for rapid assimilation and transmission to the target organs. Nerve gases are more or less fat-soluble and can penetrate the outer layers of the skin. However, it takes some time before the poison reaches the deeper blood vessels. Consequently, the first symptoms may not appear until 20-30 minutes after the initial exposure. Chemically, nerve gases act by binding to an enzyme in the body of the victim, acetylcholinesterase, which inhibits this vital enzyme's normal biological activity in the cholinergic nervous system. Acetylcholinesterase terminates nerve impulse transmission at cholinergic synapses by hydrolyzing the neurotransmitter acetylcholine to acetate and choline. Organophosphorus compounds, such as insecticides and nerve gases, inhibit acetylcholinesterase, which inhibition results in a build up of acetylcholine, thereby causing constant transmission of nerve signals.

Atropine has historically been the drug of choice to treat patients affected by nerve gases. Atropine, however, is toxic and has numerous side effects, such as supraventricular or ventricular tachycardia, and ventricular fibrillation.

There is a need in the art for new methods for treating and preventing injuries caused by chemical weapons. The invention is directed to these, as well as other, important ends.

Summary of the Invention

The invention provides safe and effective methods for preventing one or more injuries caused by organophosphorus compounds by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The at least one cholinesterase inhibitor can be administered prior to the patient's exposure to the chemicals. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

The invention provides safe and effective methods for preventing one or more injuries caused by chemical weapons by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The at least one cholinesterase inhibitor can be administered prior to the patient's exposure to the chemical weapons. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

The invention provides safe and effective methods for treating one or more injuries in patients exposed to chemicals (e.g., organophosphorus compounds, chemical weapons and the like) by administering to the patient a therapeutically effective amount of at least one cholinesterase inhibitor. In one embodiment, the cholinesterase inhibitor is donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

The invention is described in more detail below.

Detailed Description of the Invention

The invention provides methods for preventing injuries caused by organophosphorus compounds by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The cholinesterase inhibitor is preferably administered prior to the patient's exposure to the organophosphorus compounds. The organophosphorus compounds can be gases, liquids and/or solids. Gases includes aerosols. Exemplary organophosphorus compounds include agricultural compounds, chemical weapons, and the like. Exemplary agricultural compounds are pesticides, insecticides, herbicides, fungicides, and the like.

The invention provides methods for preventing injuries caused by chemical weapons by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor. The cholinesterase inhibitor is preferably administered prior to the patient's exposure to the chemical weapons. The chemical weapons can be gases, liquids and/or solids. The chemical weapons can be any in the art. In one embodiment, the chemical weapons are nerve gases. Nerve gases are organophosphorus compounds. Exemplary nerve gases are G gases, V gases, lewisite (i.e., L), and the like. G gases can include, for example, soman (i.e., GD), tabun (i.e., GA), sarin (i.e., GB), GF (i.e., cyclohexyl methylphosphono-fluoridate), GE, and the like. V-gases can include, for example, VX (i.e., O-ethyl S-diisopropylaminomethyl methylphosphonothiolate), VE, VG, VM, and the like.

Injuries caused by organophosphorus compounds (e.g., chemical weapons, agricultural compounds, and the like) can include any injury resulting from the inhibition of normal acetylcholinesterase activity which leads to a build-up of acetylcholine at cholinergic synapses. Such injuries can include, for example, blurred vision, sore eyes, teary eyes, runny nose, increased salivation, chest pains, nausea, vomiting, tremors, involuntary secretions, loss of consciousness, convulsions, bronchospasms, paralysis, ataxia, respiratory failure, and death.

In the methods of preventing injuries caused by organophosphorus compounds, such as chemical weapons or agricultural compounds, the cholinesterase inhibitors can be taken prophylatically when there is a potential or an expected exposure to the organophosphorus compounds. In one embodiment, the cholinesterase inhibitors can be taken anywhere from 30 minutes to 24 hours prior to exposure to the organophosphorus compounds; or from about 1 hour to about 22 hours prior to exposure to the organophosphorus compounds; or from about 2 hours to about

20 hours prior to exposure to the organophosphorus compounds; or from about 3 hours to about 12 hours prior to exposure to the organophosphorus compounds.

In the event the patient is exposed to the organophosphorus compounds, the cholinesterase inhibitors will provide safe and effective protection from injuries generally caused by the organophosphorus compounds. "Preventing" and "protection" means that no injuries result from the patient's exposure to the organophosphorus compounds or that the severity or intensity of the injuries that result from the patient's exposure to the organophosphorus compounds is reduced or minimized when compared to the injuries that would have resulted absent prophylactic treatment with the cholinesterase inhibitors.

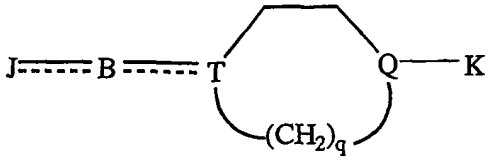
In the event the patient is not exposed to the organophosphorus compounds, the cholinesterase inhibitors will not cause any significant side effects and will simply be metabolized and eliminated by the patient's body.

In another embodiment, the invention provides methods for treating injuries in patients exposed to organophosphorus compounds, such as chemical weapons, by administering a therapeutically effective amount of at least one cholinesterase inhibitor. The organophosphorus compounds can be gases, liquids or solids. The organophosphorus compounds can be, for example, agricultural chemicals, chemical weapons, and the like.

"Patient" refers to animals, preferably mammals, more preferably humans. "Patient" includes adults and children. The "patient" can be civilian or military.

The cholinesterase inhibitor can be any in the art. Exemplary cholinesterase inhibitors include donepezil, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine (e.g., huprezine A), metrifonate, heptastigmine, edrophonium, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, TAK-147 (i.e., 3-[1-(phenylmethyl)-4-piperidinyl]-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone fumarate or other salts thereof), T-82, upreazine, and the like. In the methods described herein, one or more cholinesterase inhibitors can be used. In one embodiment, one cholinesterase inhibitor is used. In another embodiment, donepezil, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof and a second cholinesterase inhibitor is used in the methods of the invention.

In one embodiment, the cholinesterase inhibitor can be a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is

(a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) C_6H_5-CO-$CH(CH_3)$-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl group; or

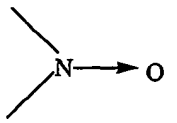
(e) a group of R^{21}-CH=CH-, in which R^{21} is hydrogen or a lower alkoxycarbonyl group;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, -CO-NR^5-$(CHR^{22})_r$-, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, =$(CH-CH=CH)_b$-,=CH-$(CH_2)_c$-, =$(CH-CH)_d$=, -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -$CH(CH_3)$-CO-NH-CH_2-, -CH=CH=CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxycarbonyl;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

Q is nitrogen, carbon or



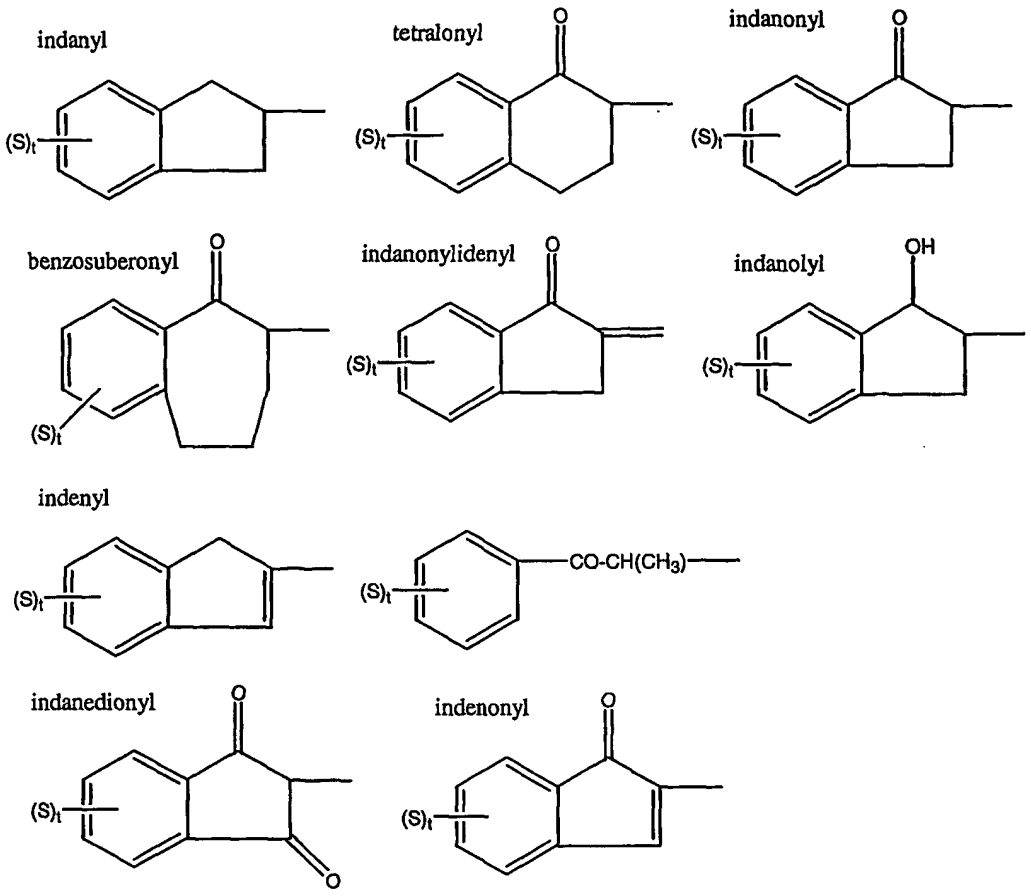
;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and

 is a single bond or a double bond.

In the compound of formula I, J is preferably (a) or (b), more preferably (b). In the definition of (b), a monovalent group (2), (3) and (5) and a divalent group (2) are preferred. The group (b) preferably includes, for example, the groups having the formulae shown below:



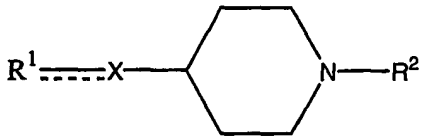
wherein t is an integer of about 1 to about 4; and each S is independently hydrogen or a substituent, such as a lower alkyl having 1 to 6 carbon atoms or a lower alkoxy having 1 to 6 carbon atoms. Among the substituents, methoxy is most preferred. The phenyl is most preferred to have 1 to 3 methoxy groups thereon. $(S)_t$ can form methylene dioxy groups or ethylene dioxy groups on two adjacent carbon atoms of the phenyl group. Of the above groups, indanonyl, indanedionyl and indenyl, optionally having substituents on the phenyl, are the most preferred.

In the definition of B, $-(CHR^{22})_r-$, $-CO-(CHR^{22})_r-$, $=(CH-CH=CH)_b-$, $=CH-(CH_2)_c-$ and $=(CH-CH)_d=$ are preferable. The group of $-(CHR^{22})_r-$ in which R^{22} is hydrogen and r is an integer of 1 to 3, and the group of $=CH-(CH_2)_c-$ are most preferable. The preferable groups of B can be connected with (b) of J, in particular (b)(2).

The ring containing T and Q in formula I can be 5-, 6- or 7-membered. It is preferred that Q is nitrogen, T is carbon or nitrogen, and q is 2; or that Q is nitrogen, T is carbon, and q is 1 or 3; or that Q is carbon, T is nitrogen and q is 2.

It is preferable that K is a phenyl, arylalkyl, cinnamyl, phenylalkyl or a phenylalkyl having a substituent(s) on the phenyl.

In another embodiment, the compounds of formula I are the compounds of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R^3-CH=C-, where R^3 is a hydrogen atom or a lower alkoxycarbonyl group;

X is $-(CH_2)_n-$, $-C(O)-(CH_2)_n-$, $-N(R^4)-(CH_2)_n-$, $-C(O)-N(R^5)-(CH_2)_n-$, $-CH=CH-(CH_2)_n-$, $-O-C(O)-O-(CH_2)_n-$, $-O-C(O)-NH-(CH_2)_n-$, $-CH=CH-CH=CO-$, $-NH-C(O)-(CH_2)_n-$, $-CH_2-C(O)-NH-(CH_2)_n-$, $-(CH_2)_2-C(O)-NH-(CH_2)_n-$, $-CH(OH)-(CH_2)_n-$, $-C(O)-CH=CH-CH_2-$, $-C(O)-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-C(O)-NH-CH_2-$, $-CH=CH-C(O)-NH-(CH_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxycarbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

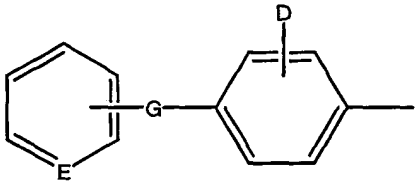
⁻⁻⁻⁻⁻ is a single bond or a double bond.

The term "lower alkyl group" as used herein means a straight or branched alkyl group having 1 to 6 carbon atoms. Exemplary "lower alkyl groups" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl (amyl), isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, hexyl, isohexyl, 1-methylpentyl, 2-methyl-pentyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 2,2-dimethylbutyl, 1,3-dimthyl-butyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, and the like. The lower alkyl group is preferably methyl, ethyl, propyl or isopropyl; more preferably methyl.

Specific examples of the substituents for the substituted or unsubstituted phenyl, pyridyl, pyrazyl, quinolyl, indanyl, cyclohexyl, quinoxalyl and furyl groups in the definition of R^1 include

lower alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, and tert-butyl groups; lower alkoxy groups corresponding to the above-described lower alkyl groups, such as methoxy and ethoxy groups; a nitro group; halogen atoms, such as chlorine, fluorine and bromine; a carboxyl group; lower alkoxycarbonyl groups corresponding to the above-described lower alkoxy groups, such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, n-propoxycarbonyl, and n-butyloxycarbonyl groups; an amino group; a lower monoalkylamino group; a lower dialkylamino group; a carbamoyl group; acylamino groups derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, such as acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, and pivaloylamino groups; cycloalkyloxycarbonyl groups, such as a cyclohexyloxycarbonyl group; lower alkylaminocarbonyl groups, such as methylaminocarbonyl and ethylaminocarbonyl groups; lower alkylcarbonyloxy groups corresponding to the above-defined lower alkyl groups, such as methylcarbonyloxy, ethylcarbonyloxy, and n-propylcarbonyloxy groups; halogenated lower alkyl groups, such as a trifluoromethyl group; a hydroxyl group; a formyl group; and lower alkoxy lower alkyl groups, such as ethoxymethyl, methoxymethyl and methoxyethyl groups. The "lower alkyl groups" and "lower alkoxyl groups" in the above description of the substituent include all the groups derived from the above-mentioned groups. The substituent can be one to three of them, which can be the same or different.

When the substituent is a phenyl group, the following group is within the scope of the substituted phenyl group:



wherein G is -C(O)-, -O-C(O)-, -O-, $-CH_2$-NH-C(O)-, $-CH_2$-O-, $-CH_2-SO_2$-, -CH(OH)-, or $-CH_2$-S(→O)-; E is a carbon or nitrogen atom; and D is a substituent.

Preferred examples of the substituents (i.e., "D") for the phenyl group include lower alkyl, lower alkoxy, nitro, halogenated lower alkyl, lower alkoxycarbonyl, formyl, hydroxyl, and lower alkoxy lower alkyl groups, halogen atoms, and benzyol and benzylsulfonyl groups. The substituent can be two or more of them, which can be the same or different.

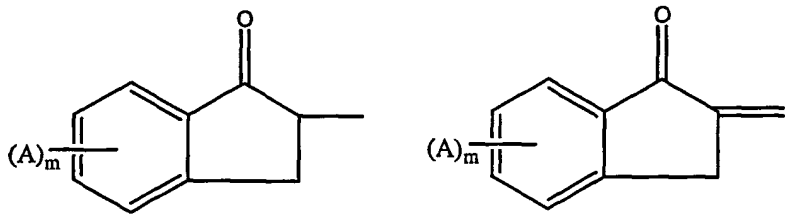
Preferred examples of the substituent for the pyridyl group include lower alkyl and amino groups and halogen atoms.

Preferred examples of the substituent for the pyrazyl group include lower alkoxycarbonyl, carboxyl, acylamino, carbamoyl, and cycloalkyloxycarbonyl groups.

With respect to R^1, the pyridyl group is preferably a 2-pyridyl, 3-pyridyl, or 4-pyridyl group; the pyrazyl group is preferably a 2-pyrazinyl group; the quinolyl group is preferably a 2-quinolyl or 3-

quinolyl group; the quinoxalinyl group is preferably a 2-quinoxalinyl or 3-quinoxalinyl group; and the furyl group is preferably a 2-furyl group.

Examples of preferred monovalent or divalent groups derived from an indanone having an unsubstituted or substituted phenyl ring include those represented by formulas (A) and (B):

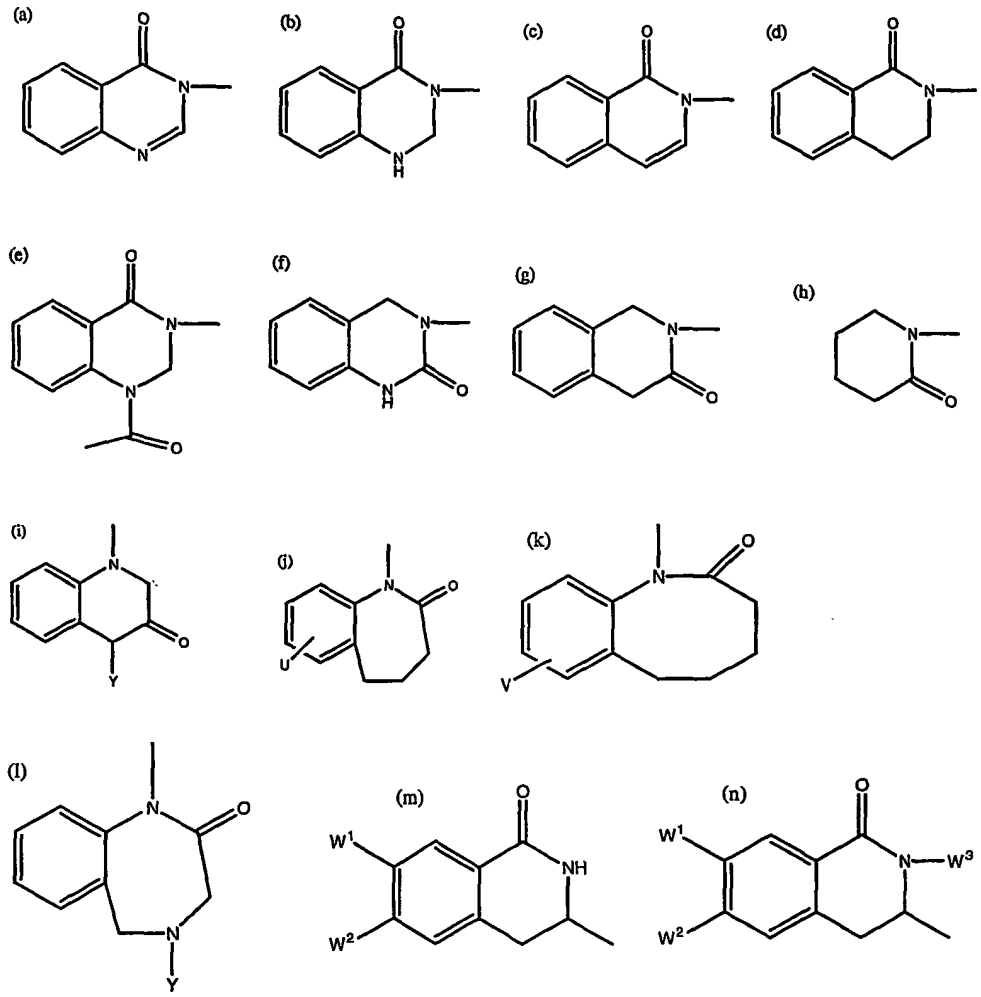


(A) (B)

where m is an integer of from 1 to 4, and each A is independently a hydrogen atom, a lower alkyl group, a lower alkoxy group, a nitro group, a halogen atom, a carboxyl group, a lower alkoxycarbonyl group, an amino group, a lower monoalkylamino group, a lower dialkylamino group, a carbamoyl group, an acylamino group derived from aliphatic saturated monocarboxylic acids having 1 to 6 carbon atoms, a cycloalkyloxycarbonyl group, a lower alkylaminocarbonyl group, a lower alkylcarbonyloxy group, a halogenated lower alkyl group, a hydroxyl group, a formyl group, or a lower alkoxy lower alkyl group; preferably a hydrogen atom, a lower alkyl group or a lower alkoxy group; most preferably the indanone group is unsubstituted or substituted with 1 to 3 methoxy groups.

Examples of the monovalent group derived from a cyclic amide compound include quinazolone, tetrahydroisoquinolinone, tetrahydrobenzodiazepinone, and hexahydrobenzazocinone. However, the monovalent group can be any one having a cyclic amide group in the structural formula thereof, and is not limited to the above-described specific examples. The cyclic amide group can be one derived from a monocyclic or condensed heterocyclic ring. The condensed heterocyclic ring is preferably one formed by condensation with a phenyl ring. In this case, the phenyl ring can be substituted with a lower alkyl group having 1 to 6 carbon atoms, preferably a methyl group, or a lower alkoxy group having 1 to 6 carbon atoms, preferably a methoxy group.

Preferred examples of the monovalent group include the following:



In the above formulae, Y is a hydrogen atom or a lower alkyl group; V and U are each a hydrogen atom or a lower alkoxy group (preferably dimethoxy); W^1 and W^2 are each a hydrogen atom, a lower alkyl group, or a lower alkoxy group; and W^3 is a hydrogen atom or a lower alkyl group. The right hand ring in formulae (j) and (l) is a 7-membered ring, while the right hand ring in formula (k) is an 8-membered ring.

The most preferred examples of the above-defined R^1 include a monovalent group derived from an indanone having an unsubstituted or substituted phenyl group and a monovalent group derived from a cyclic amide compound.

The most preferred examples of the above-defined X include $-(CH_2)_n-$, an amide group, or groups represented by the above formulae where n is 2. Thus, it is most preferred that any portion of a group represented by the formula R^1------ X—— have a carbonyl or amide group.

The substituents involved in the expressions "a substituted or unsubstituted phenyl group" and "a substituted or unsubstituted arylalkyl group" in the above definition of R^2 are the same substituents as those described for the above definitions of a phenyl group, a pyridyl group, a pyrazyl

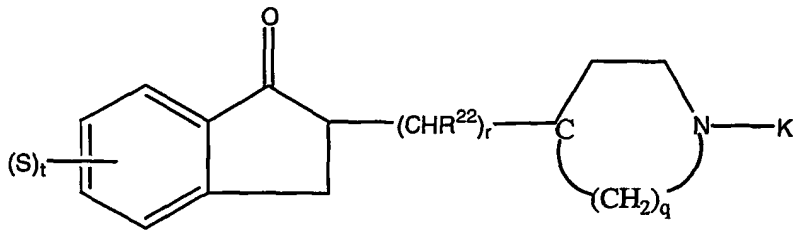
group, a quinolyl group, an indanyl group, a cyclohexyl group, a quinoxalyl group or a furyl group in the definition of R^1.

The term "arylalkyl group" is intended to mean an unsubstituted benzyl or phenethyl group or the like.

Specific examples of the pyridylmethyl group include 2-pyridylmethyl, 3-pyridylmethyl, and 4-pyridylmethyl groups.

Preferred examples of R^2 include benzyl and phenethyl groups. The symbol ------ means a double or single bond. The bond is a double bond only when R^1 is the divalent group (B) derived from an indanone having an unsubstituted or substituted phenyl ring, while it is a single bond in other cases.

In another embodiment, the compound of formula II is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:

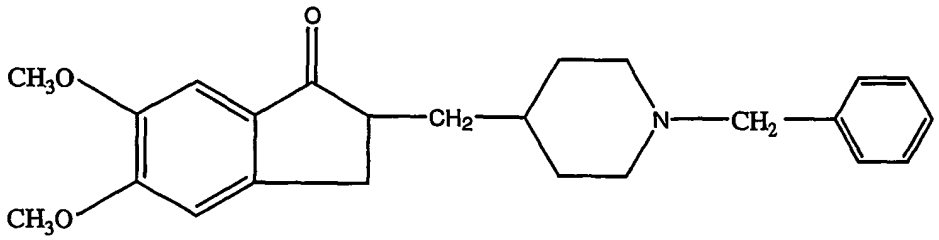


III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

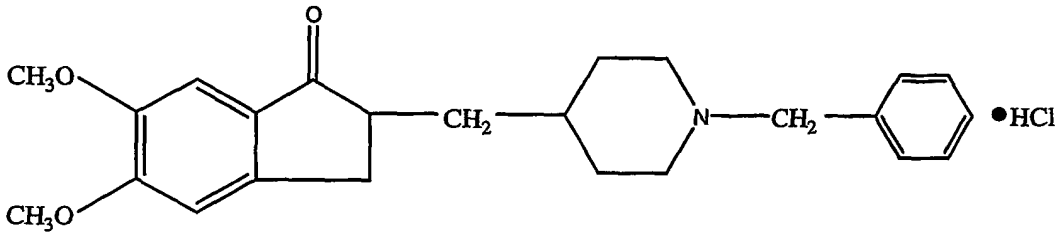
In other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methyl-piperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; a stereoisomer and/or a pharmaceutically acceptable salt thereof.

In other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, which is represented by formula IV:



IV.

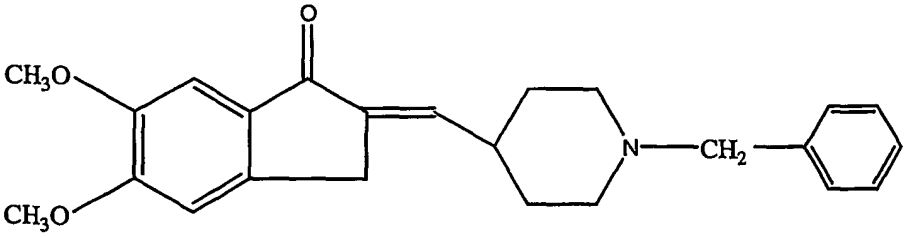
In still other embodiments, the compound of formula III is 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride or a stereoisomer thereof, which is also known as donepezil hydrochloride or ARICEPT® (Eisai Inc., Teaneck, NJ), and which is represented by formula IVa:



IVa.

The compounds of the invention can have an asymmetric carbon atom(s), depending upon the substituents, and can have stereoisomers, which are within the scope of the invention. For example, donepezil or pharmaceutically acceptable salts thereof can be in the forms described in Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference herein in their entirety.

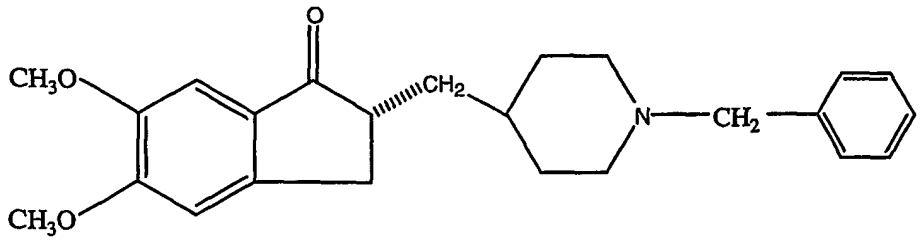
Japanese Patent Application No. 4-187674 describes a compound of formula V:



V

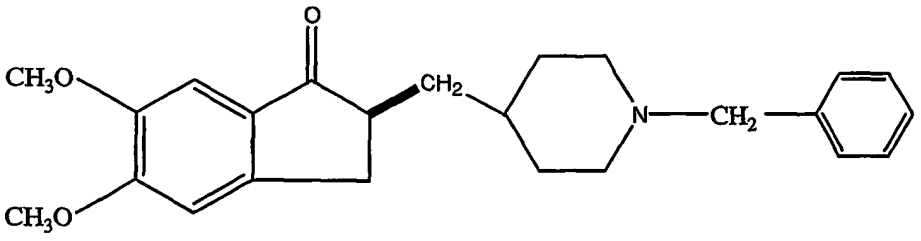
which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt.

Japanese Patent Application No. 4-21670 describes compounds of formula VI:



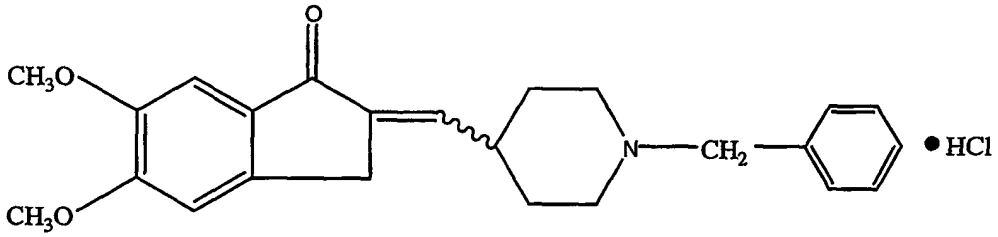
VI

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VII:



VII

which can be in the form of a pharmaceutically acceptable salt, such as a hydrochloride salt; and compounds of formula VIII:



VIII.

The cholinesterase inhibitors can be administered in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts are well known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide and phosphate; and those of organic acids, such as formate, acetate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate. When certain substituents are selected, the compounds of the invention can form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any other pharmaceutically acceptable salt.

The cholinesterase inhibitors can be prepared by processes known in the art and described, for example, in U.S. Patent No. 4,895,841, WO 98/39000, and Japanese Patent Application Nos. 4-187674 and 4-21670, the disclosures of which are incorporated by reference herein in their entirety.

Donepezil hydrochloride, a preferred cholinesterase inhibitor for use in the methods described herein, is commercially available as ARICEPT® from Eisai Inc., Teaneck, NJ.

The dosage regimen for treating and preventing the injuries described herein with the cholinesterase inhibitors can be selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the drugs, and whether a drug delivery system is used.

The cholinesterase inhibitors can be administered in doses of about 0.1 milligram to about 300 milligrams per day, preferably about 1 milligram to about 100 milligrams per day, more preferably about 5 milligrams to about 10 milligrams per day. The doses can be administered in one to four portions over the course of a day, preferably once a day. One skilled in the art will recognize that when the cholinesterase inhibitors are administered to children, the dose can be smaller than the dose administered to adults, and that the dose can be dependent upon the size and weight of the patient. A child can be administered the cholinesterase inhibitors in doses of about 0.1 milligrams to about 15 milligrams per day, preferably about 0.5 milligrams to about 10 milligrams per day, more preferably about 1 milligram to about 3 milligrams per day.

In other embodiments of the methods described herein, donepezil hydrochloride, which is commercially available as ARICEPT® (Eisai Inc., Teaneck, NJ), can be administered as tablets containing either 5 milligrams donepezil hydrochloride or 10 milligrams donepezil hydrochloride. One skilled in the art will appreciate that when donepezil hydrochloride is administered to children, the dose can be smaller than the dose that is administered to adults.

The cholinesterase inhibitors can be administered orally, topically, parenterally, by inhalation (nasal or oral), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral includes subcutaneous, intravenous, intramuscular, intrasternal injection, or infusion techniques. Preferably, the cholinesterase inhibitors are orally administered as tablets. When administered to children, the cholinesterase inhibitors are preferably orally administered in a liquid dosage form.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, of the cholinesterase inhibitors can be formulated according to the art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxyethylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like) and preservatives. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be

used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil can be used including synthetic mono- or diglycerides, in addition, fatty acids, such as oleic acid, can be used in the preparation of injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration of the cholinesterase inhibitors can include chewing gum, capsules, tablets, sublingual tablets, powders, granules and gels; preferably tablets. In such solid dosage forms, the active compound can be admixed with one or more inert diluents such as lactose or starch. As is normal practice, such dosage forms can also comprise other substances including lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms can also comprise buffering agents. The tablets can be prepared with enteric or film coatings, preferably film coatings.

Sublingual administration refers to the administration of the cholinesterase inhibitors in the mouth (e.g., under the tongue, between the cheek and gum, between the tongue and roof of the mouth). The highly vascular mucosal lining in the mouth is a convenient location for the cholinesterase inhibitors to be administered into the body. To make tablets, the cholinesterase inhibitors can be admixed with pharmaceutically acceptable carriers known in the art such as, for example, vehicles (e.g., lactose, white sugar, mannitol, glucose, starches, calcium carbonate, crystalline cellulose, silicic acid, and the like), binders (e.g., water, ethanol, myranol, glucose solution, starch solution, gelatin solution, polyvinylpyrrolidone, and the like), disintegrators (e.g., dry starch, sodium, alginate, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium laurylsulfate, stearic monoglyceride, starches, lactose, and the like), absorption promoters (e.g., quaternary ammonium base, sodium laurylsulfate, and the like), wetting agents (e.g. glycerin, starches, and the like), lubricants (e.g., stearates, polyethylene glycol, and the like), and flavoring agents (e.g., sweeteners). The tablets can be in the form of a conventional tablet, a molded tablet, a wafer and the like.

Liquid dosage forms for oral administration of the cholinesterase inhibitors can include pharmaceutically acceptable emulsions, solutions, sublingual solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents. To make sublingual solutions, the cholinesterase inhibitors can be admixed with various carriers, excipients, pH adjusters, and the like (e.g., water, sugar, lactic acid, acetic acid, fructose, glucose, saccharin, polyethylene glycol, propylene glycol, alcohol, bentonite, tragacanth, gelatin, alginates, aspartame, sorbitol, methylparaben, propylparaben, sodium benzoate, artificial flavoring and coloring agents).

For administration by inhalation, the cholinesterase inhibitors can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by inhalation, the cholinesterase inhibitors can be administered in the form of a dry powder composition or in the form of a liquid spray.

Suppositories for rectal administration of the cholinesterase inhibitors can be prepared by mixing the active compounds with suitable nonirritating excipients such as cocoa butter and polyethylene glycols that are solid at room temperature and liquid at body temperature.

For topical administration to the epidermis, the cholinesterase inhibitors can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The cholinesterase inhibitors can also be administered via iontophoresis. Ointments, creams and lotions can be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively, ointments, creams and lotions can be formulated with an aqueous or oily base and can also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the cholinesterase inhibitors can be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions can contain polyethylene glycol 400. To form ointments, the cholinesterase inhibitors can be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the transdermally administrable compositions for topical application.

The cholinesterase inhibitors can also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the cholinesterase inhibitors and laminated to an impermeable backing. For example, the cholinesterase inhibitors can be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches can include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

Each of the patents, patent applications, and publications cited herein are incorporated by reference herein in their entirety.

It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

Claims

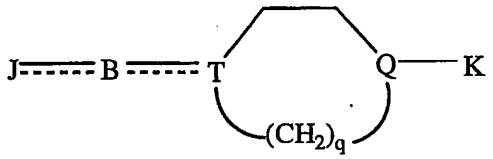
What is claimed is:

1. A method for preventing an injury caused by an organophosphorus compound by administering to a patient in need thereof a therapeutically effective amount of at least one cholinesterase inhibitor.

2. The method of claim 1, wherein the cholinesterase inhibitor is administered to the patient prior to exposure to the organophosphorus compound.

3. The method of claim 1, wherein the cholinesterase inhibitor is donepezil, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, 3-(1-(phenylmethyl)-4-piperidinyl)-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone, T-82, upreazine, or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is

(a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) C_6H_5-CO-$CH(CH_3)$-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl group; or

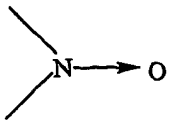
(e) a group of R^{21}-CH=CH-, in which R^{21} is hydrogen or a lower alkoxycarbonyl group;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, -CO-NR^5-$(CHR^{22})_r$-, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, =$(CH-CH=CH)_b$-, =CH-$(CH_2)_c$-, =$(CH-CH)_d$=, -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -$CH(CH_3)$-CO-NH-CH_2-, -CH=CH=CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxycarbonyl;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

Q is nitrogen, carbon or



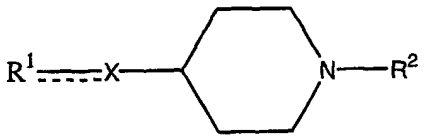
;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and

 is a single bond or a double bond.

5. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R^3-CH=C-, where R^3 is a hydrogen atom or a lower alkoxycarbonyl group;

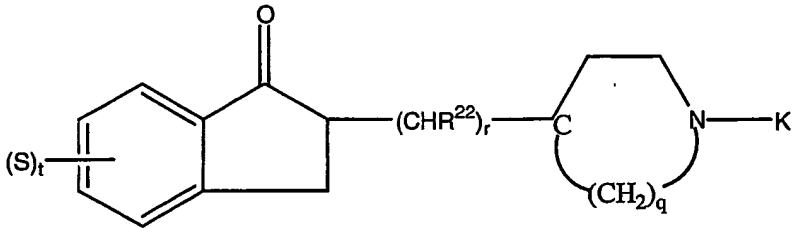
X is $-(CH_2)_n-$, $-C(O)-(CH_2)_n-$, $-N(R^4)-(CH_2)_n-$, $-C(O)-N(R^5)-(CH_2)_n-$, $-CH=CH-(CH_2)_n-$, $-O-C(O)-O-(CH_2)_n-$, $-O-C(O)-NH-(CH_2)_n-$, $-CH=CH-CH=CO-$, $-NH-C(O)-(CH_2)_n-$, $-CH_2-C(O)-NH-(CH_2)_n-$, $-(CH_2)_2-C(O)-NH-(CH_2)_n-$, $-CH(OH)-(CH_2)_n-$, $-C(O)-CH=CH-CH_2-$, $-C(O)-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-C(O)-NH-CH_2-$, $-CH=CH-C(O)-NH-(CH_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxycarbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

⎓ is a single bond or a double bond.

6. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:

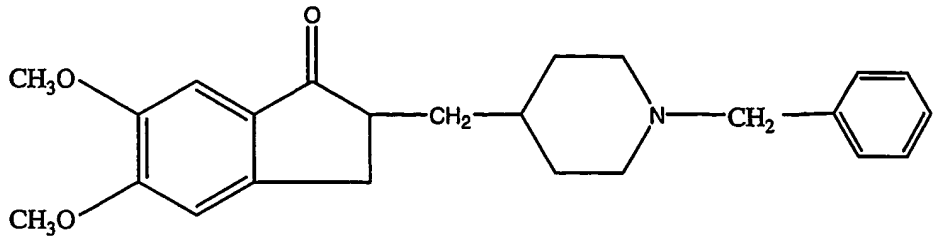


III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

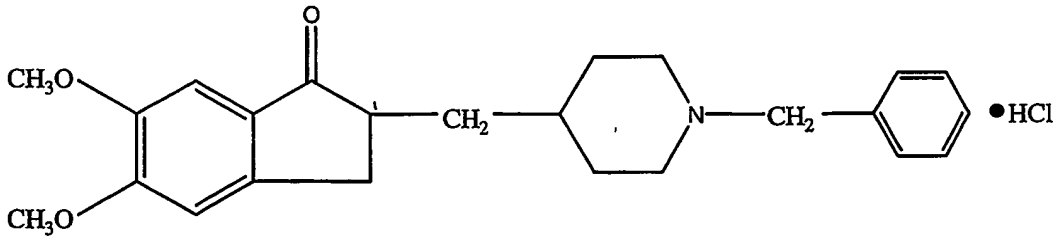
7. The method of claim 1, wherein the cholinesterase inhibitor 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methyl-piperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; a stereoisomer and/or a pharmaceutically acceptable salt thereof.

8. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula IV, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



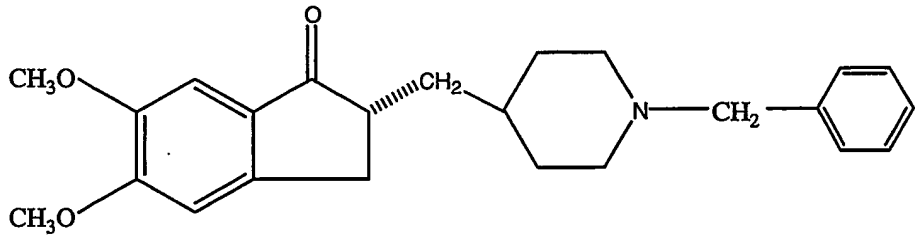
IV.

9. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula IVa or a stereoisomer thereof:



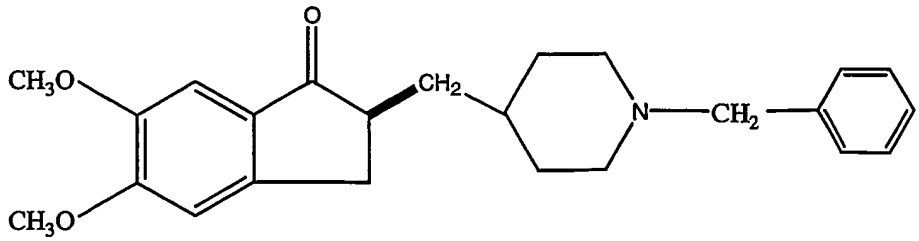
IVa.

10. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula VI or a pharmaceutically acceptable salt thereof:



VI.

11. The method of claim 1, wherein the cholinesterase inhibitor is a compound of formula VII or a pharmaceutically acceptable salt thereof:



VII.

12. A methods for preventing an injury caused by a chemical weapon in a patient in need thereof comprising administering a therapeutically effective amount of at least one cholinesterase inhibitor prior to the patient.

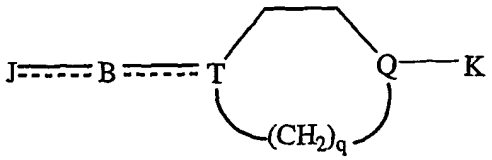
13. The method of claim 12, comprising administering the cholinesterase inhibitor to the patient prior to exposure to the chemical weapon.

14. The method of claim 12, wherein the chemical weapon is a nerve gas.

15. The method of claim 14, wherein the nerve gas is a G gas, a V gas, or lewisite.

16. The method of claim 12, wherein the cholinesterase inhibitor is donepezil, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, 3-(1-(phenylmethyl)-4-piperidinyl)-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone, T-82, upreazine, or a pharmaceutically acceptable salt thereof.

17. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is

(a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) C_6H_5-CO-$CH(CH_3)$-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl group; or

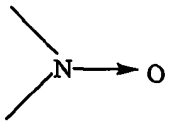
(e) a group of R^{21}-CH=CH-, in which R^{21} is hydrogen or a lower alkoxycarbonyl group;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, -CO-NR^5-$(CHR^{22})_r$-, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, -CH_2-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, =$(CH-CH=CH)_b$-, =CH-$(CH_2)_c$-, =$(CH-CH)_d$=, -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -$CH(CH_3)$-CO-NH-CH_2-, -CH=CH=CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxycarbonyl;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

Q is nitrogen, carbon or



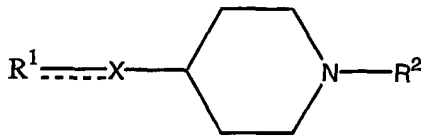
;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and

 is a single bond or a double bond.

18. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R^3-CH=C-, where R^3 is a hydrogen atom or a lower alkoxycarbonyl group;

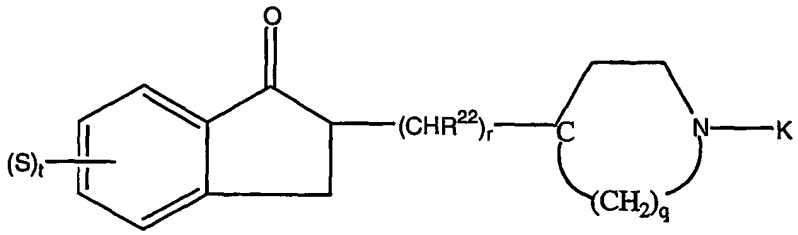
X is $-(CH_2)_n-$, $-C(O)-(CH_2)_n-$, $-N(R^4)-(CH_2)_n-$, $-C(O)-N(R^5)-(CH_2)_n-$, $-CH=CH-(CH_2)_n-$, $-O-C(O)-O-(CH_2)_n-$, $-O-C(O)-NH-(CH_2)_n-$, $-CH=CH-CH=CO-$, $-NH-C(O)-(CH_2)_n-$, $-CH_2-C(O)-NH-(CH_2)_n-$, $-(CH_2)_2-C(O)-NH-(CH_2)_n-$, $-CH(OH)-(CH_2)_n-$, $-C(O)-CH=CH-CH_2-$, $-C(O)-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-C(O)-NH-CH_2-$, $-CH=CH-C(O)-NH-(CH_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxycarbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

------ is a single bond or a double bond.

19. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:

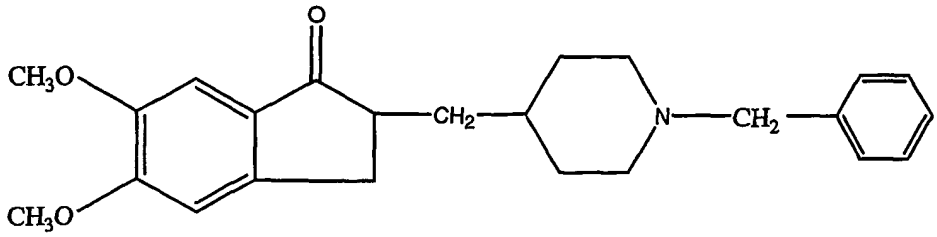


III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

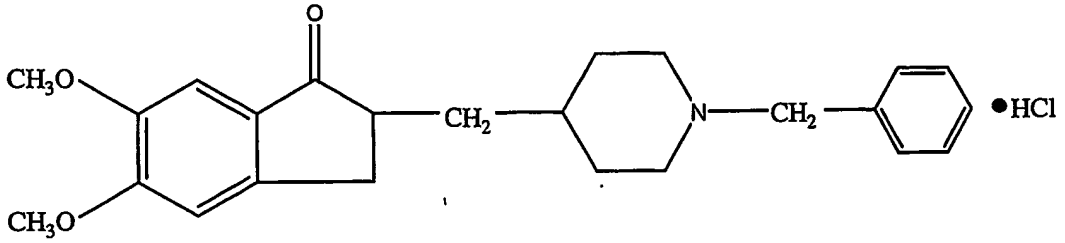
20. The method of claim 12, wherein the cholinesterase inhibitor 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methyl-piperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; a stereoisomer and/or a pharmaceutically acceptable salt thereof.

21. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula IV, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



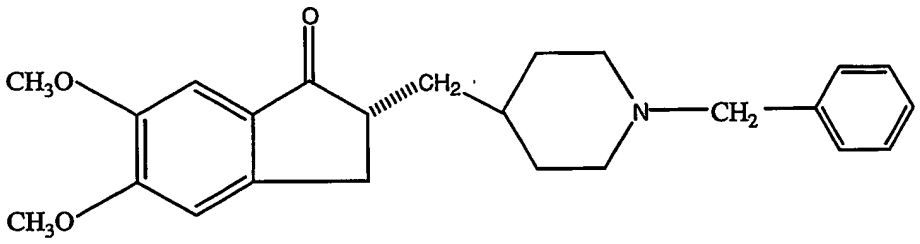
IV.

22. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula IVa or a stereoisomer thereof:



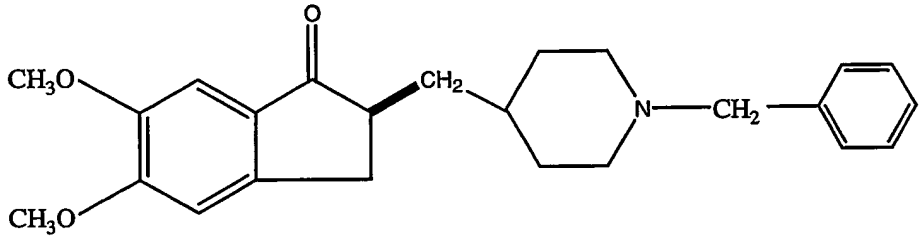
IVa.

23. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula VI or a pharmaceutically acceptable salt thereof:



VI.

24. The method of claim 12, wherein the cholinesterase inhibitor is a compound of formula VII or a pharmaceutically acceptable salt thereof:



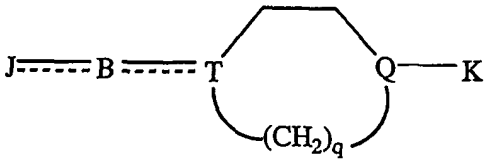
VII.

25. A method for treating an injury in a patient exposed to a chemical compound comprising administering a therapeutically effective amount of at least one cholinesterase inhibitor.

26. The method of claim 25, wherein the chemical compound is a chemical weapon or an agricultural chemical.

27. The method of claim 25, wherein the cholinesterase inhibitor is donepezil, tacrine, physostigmine, pyridostigmine, neostigmine, rivastigmine, galantamine, citicoline, velnacrine, huperzine, metrifonate, heptastigmine, edrophonium, phenserine, tolserine, phenethylnorcymserine, ganstigmine, epastigmine, 3-(1-(phenylmethyl)-4-piperidinyl)-1-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-1-propanone, T-82, upreazine, or a pharmaceutically acceptable salt thereof.

28. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula I, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



I

wherein J is

(a) a substituted or unsubstituted group selected from the group consisting of (1) phenyl, (2) pyridyl, (3) pyrazyl, (4) quinolyl, (5) cyclohexyl, (6) quinoxalyl, and (7) furyl;

(b) a monovalent or divalent group, in which the phenyl can have one or more substituents selected from (1) indanyl, (2) indanonyl, (3) indenyl, (4) indenonyl, (5) indanedionyl, (6) tetralonyl, (7) benzosuberonyl, (8) indanolyl, and (9) C_6H_5-CO-$CH(CH_3)$-;

(c) a monovalent group derived from a cyclic amide compound;

(d) a lower alkyl group; or

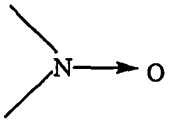
(e) a group of R^{21}-CH=CH-, in which R^{21} is hydrogen or a lower alkoxycarbonyl group;

B is -$(CHR^{22})_r$-, -CO-$(CHR^{22})_r$-, -NR^4-$(CHR^{22})_r$-, -CO-NR^5-$(CHR^{22})_r$-, -CH=CH-$(CHR^{22})_r$-, -OCOO-$(CHR^{22})_r$-, -OOC-NH-$(CHR^{22})_r$-, -NH-CO-$(CHR^{22})_r$-, $-CH_2$-CO-NH-$(CHR^{22})_r$-, -$(CH_2)_2$-NH-$(CHR^{22})_r$-, -CH(OH)-$(CHR^{22})_r$-, =$(CH-CH=CH)_b$-, =CH-$(CH_2)_c$-, =$(CH-CH)_d$=, -CO-CH=CH-CH_2-, -CO-CH_2-CH(OH)-CH_2-, -$CH(CH_3)$-CO-NH-CH_2-, -CH=CH=CO-NH-$(CH_2)_2$-, -NH-, -O-, -S-, a dialkylaminoalkyl-carbonyl or a lower alkoxycarbonyl;

wherein R^4 is hydrogen, lower alkyl, acyl, lower alkylsulfonyl, phenyl, substituted phenyl, benzyl, or substituted benzyl; R^5 is hydrogen, lower alkyl or phenyl; r is zero or an integer of about 1 to about 10; R^{22} is hydrogen or methyl so that one alkylene group can have no methyl branch or one or more methyl branches; b is an integer of about 1 to about 3; c is zero or an integer of about 1 to about 9; d is zero or an integer of about 1 to about 5;

T is nitrogen or carbon;

Q is nitrogen, carbon or



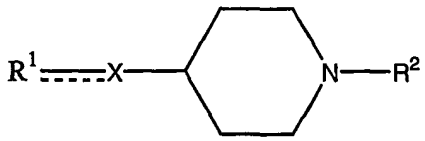
;

q is an integer of about 1 to about 3;

K is hydrogen, phenyl, substituted phenyl, arylalkyl in which the phenyl can have a substituent, cinnamyl, a lower alkyl, pyridylmethyl, cycloalkylalkyl, adamantanemethyl, furylmenthyl, cycloalkyl, lower alkoxycarbonyl or an acyl; and

 is a single bond or a double bond.

29. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula II, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:



II

wherein R^1 is a (1) substituted or unsubstituted phenyl group; (2) a substituted or unsubstituted pyridyl group; (3) a substituted or unsubstituted pyrazyl group; (4) a substituted or unsubstituted quinolyl group; (5) a substituted or unsubstituted indanyl group; (6) a substituted or unsubstituted cyclohexyl group; (7) a substituted or unsubstituted quinoxalyl group; (8) a substituted or unsubstituted furyl group; (9) a monovalent or divalent group derived from an indanone having a substituted or unsubstituted phenyl ring; (10) a monovalent group derived from a cyclic amide compound; (11) a lower alkyl group; or (12) a group of the formula R^3-CH=C-, where R^3 is a hydrogen atom or a lower alkoxycarbonyl group;

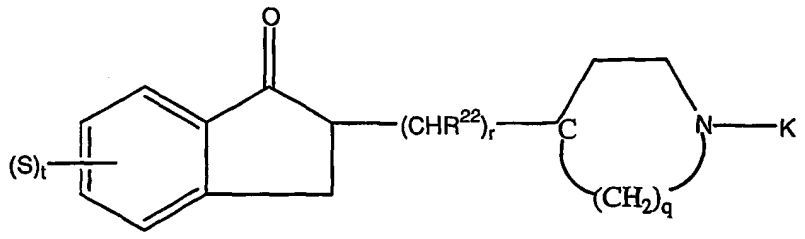
X is $-(CH_2)_n-$, $-C(O)-(CH_2)_n-$, $-N(R^4)-(CH_2)_n-$, $-C(O)-N(R^5)-(CH_2)_n-$, $-CH=CH-(CH_2)_n-$, $-O-C(O)-O-(CH_2)_n-$, $-O-C(O)-NH-(CH_2)_n-$, $-CH=CH-CH=CO-$, $-NH-C(O)-(CH_2)_n-$, $-CH_2-C(O)-NH-(CH_2)_n-$, $-(CH_2)_2-C(O)-NH-(CH_2)_n-$, $-CH(OH)-(CH_2)_n-$, $-C(O)-CH=CH-CH_2-$, $-C(O)-CH_2-CH(OH)-CH_2-$, $-CH(CH_3)-C(O)-NH-CH_2-$, $-CH=CH-C(O)-NH-(CH_2)_2-$, a dialkylaminoalkylcarbonyl group, a lower alkoxycarbonyl group;

where n is an integer of 0 to 6; R^4 is a hydrogen atom, a lower alkyl group, an acyl group, a lower alkylsulfonyl group, a substituted or unsubstituted phenyl group, or a substituted or unsubstituted benzyl group; and R^5 is a hydrogen atom a lower alkyl group or a phenyl group;

R^2 is a substituted or unsubstituted phenyl group; a substituted or unsubstituted arylalkyl group; a cinnamyl group; a lower alkyl group; a pyridylmethyl group; a cycloalkylalkyl group; an adamantanemethyl group; or a furoylmethyl group; and

 is a single bond or a double bond.

30. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula III, a stereoisomer thereof, and/or a pharmaceutically acceptable salt thereof:

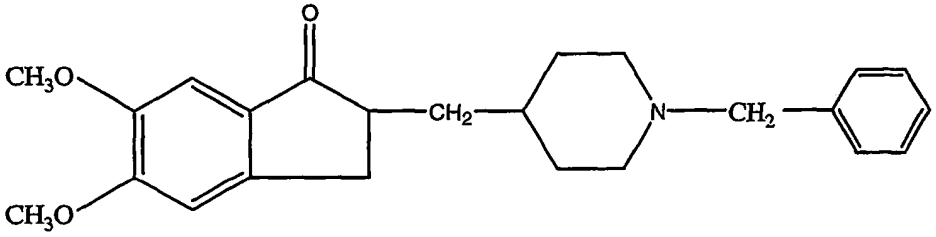


III

wherein r is an integer of about 1 to about 10; each R^{22} is independently hydrogen or methyl; K is a phenalkyl or a phenalkyl having a substituent on the phenyl ring; each S is independently a hydrogen, a lower alkyl group having 1 to 6 carbon atoms or a lower alkoxy group having 1 to 6 carbon atoms; t is an integer of 1 to 4; q is an integer of about 1 to about 3; with the proviso that $(S)_t$ can be a methylenedioxy group or an ethylenedioxy group joined to two adjacent carbon atoms of the phenyl ring.

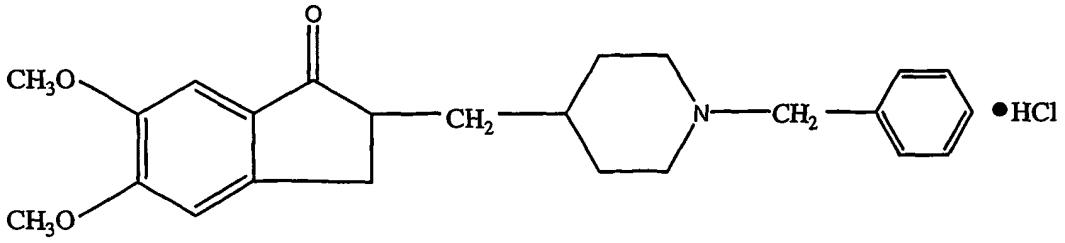
31. The method of claim 25, wherein the cholinesterase inhibitor 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-ylidenyl)methyl-piperidine; 1-benzyl-4-((5-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-diethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-methnylenedioxy-1-indanon)-2-yl)methylpiperidine; 1-(m-nitrobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-cyclohexylmethyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-(m-fluorobenzyl)-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)propylpiperidine; 1-benzyl-4-((5-isopropoxy-6-methoxy-1-indanon)-2-yl)methylpiperidine; 1-benzyl-4-((5,6-dimethoxy-1-oxoindanon)-2-yl)propenylpiperidine; a stereoisomer and/or a pharmaceutically acceptable salt thereof.

32. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula IV, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof:



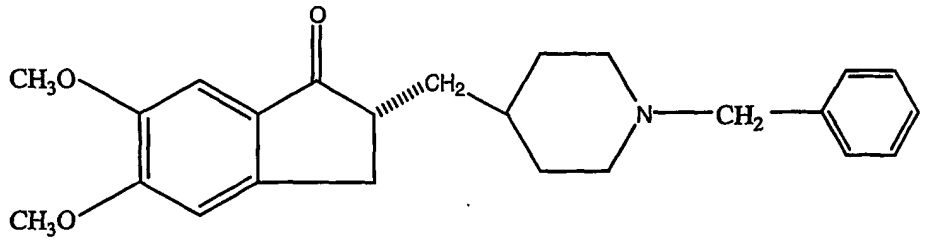
IV.

33. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula IVa or a stereoisomer thereof:



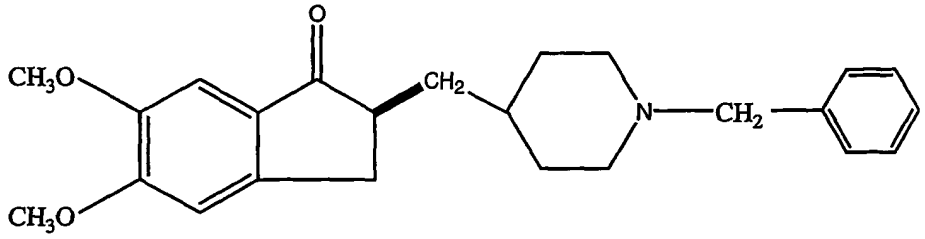
IVa.

34. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula VI or a pharmaceutically acceptable salt thereof:



VI.

35. The method of claim 25, wherein the cholinesterase inhibitor is a compound of formula VII or a pharmaceutically acceptable salt thereof:



VII.